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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,658	03/01/2004	Cheryl D. Blume	SOM700/4-4CIP2CON2DIV	9575

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,658	BLUME ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 34-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26 and 34-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Receipt of terminal disclaimer and response dated 1-25-05 is acknowledged.

Claims 24, 34-62 are pending in the instant application.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 112

Claims 26 and 34, 38-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims recite a method of treating "a condition" produced by immune system dysfunction that is associated with reduced levels of gamma-interferon production, comprising administering R(-) desmethylselegiline (DMS), wherein the administration leads to an increased production of gamma-interferon in the mammal. Instant claims are broad as they encompass a number of "conditions" that are stimulated or caused by immune dysfunction or immune deficiency.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: nature of the invention, breadth of the claims, state of the art, guidance of the specification, predictability if the art, and the working examples. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to a method of treating "a condition" produced by immune system dysfunction that is associated with reduced levels of gamma-interferon production, comprising administering R(-) desmethylselegiline (DMS), wherein the administration leads to an increased production of gamma-interferon in the mammal. The nature of the invention is extremely complex in that it encompasses anticipating multiple complex diseases or disorders and subsequently administering the instant composition. The breadth of the claims exacerbates the complex nature of the claims. The claim encompasses treating complex disorders that may have potential causes other than those disclosed in the specification. The term immune dysfunction is not necessarily manifested by one condition i.e., pathogenesis, disease or disorder. For instance, AIDS (also described in the instant invention) is a complex of diseases and conditions, which are not necessarily treatable.

State of the Art: The state of the art does not recognize the administration of compositions to treat disorders such as substance abuse, neurological conditions associated with increased monoamine oxidase, reduced dopamine uptake etc. The state of the art also recognizes treating specific infections or diseases by administering gamma -interferon or other immunomodulating interleukins or chemokines. However, the functioning of immune system in response to an infection or a disease or disorder is modulated by not one immunomodualtor molecule but is a complex interplay of several interleukins or chemokines. Further, a reduction in gamma-interferon does not necessarily result in immune system dysfunction. This is particularly evident from the

cited references (Immunology, 1996 and Shi et al, J. Immunology 2004) in the case of AIDS, which applicants claims as a condition caused by immune dysfunction and is associated with reduced gamma-interferon. Thus, the described or claimed conditions may or may not be caused by gamma-interferon reduction leading to immune dysfuntion.

Guidance of the Specification: The guidance given by the specification on how to treat the disorders is absent. Instant specification describes the effect of age on T cell function in terms of the levels of IL-2 and IFN-gamma. Further, the specification also describes the effect of DMS in restoring the levels of IL-2 and gamma-interferon. However, instant specification provides no guidance with respect to the procedure of administering instant composition to mammals for treating any or all of the disorders claimed. Instant specification also fails to provide any guidance or rationale showing that the claimed method is effective in completely treating any or all disorders produced by immune dysfunction, associated with reduced levels of gamma-IFN or to extrapolate the data provided to al immune dysfunction conditions, that are known to-date or yet to discovered.

Predictability of the Art & The Amount of Experimentation Necessary: The specification lacks guidance from the with regard to treating the claimed conditions, such that a completely effective treatment is ensured. Further, the state of the art recognizes that gamma-IFN levels need not necessarily be reduced in all immune dysfunction conditions or disorders. Thus, the lack of guidance from the specification

together with unpredictability of reduced IFN levels in all immune dysfunctions (see above references), leads to further unpredictability of the efficacy of DMS in treating conditions produced by immune system dysfuntion (associated with gamma-IFN). Therefore, the practitioner would turn to trial and error experimentation in order to determine the "conditions" caused by immune system dysfuntion (associated with gamma-IFN) in mammals that would respond to the claimed method of treatment (employing the claimed composition). Therefore, undue experimentation becomes the burden of the practitioner.

Claim Rejections - 35 USC § 103

Claims 26 and 34, 38-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over f Borbe (J. neural. Transm. Suppl. 1990) in view of Barton et al (J. Neurooncol.) and Balsa et al (Biochem. Pharmacol. 1987).

Borbe teaches desmethylselegiline (DMS) and selegiline as effective MAO-B inhibitors, which irreversibly blocks MAO-B. Borbe also teaches oral administration of DMS in rats. However, Borbe does not specifically state that DMS is used for treating "a condition produced by immune system dysfunction that is associated with gamma-interferon production", as claimed. Further, Borbe also fails to teach the claimed enantiomer or specific disease conditions.

Barton et al (Barton) analyzed neurological complications in patients suffering from Kaposi's sarcoma and observed that patients suffered neurological dysfuntion that

included neoplastic involvement of nervous system, autoimmune disorders or opportunistic infections.(abstract). Barton does not suggest any treatment for the above conditions, however, establishes a relation ship between acquired immune deficiency syndrome, autoimmune disorders, nervous system dysfunction and opportunistic infections.

Balsa et al teaches monoamine oxidase activities in lymphocytes (L) and granulocytes (G), particularly against 5-hydroxytryptamine, benzylamine, beta-phenyl ethylamine etc., as substrates. Balsa et al conclude from their experiments with deprenyl that monoamine oxidase (MAO) activity present in both L and G is predominantly of MAO-B form. Thus, Balsa shows the activity of MAO-B in lymphocytes and granulocytes, the cell types that play a key role in immune system function and Barton teaches that immune deficiency is related to conditions such as cancer, neurological dysfunction, infection and AIDS. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use DMS of Borbe for reducing the MAO-B activity in lymphocytes and granulocytes, which in turn play an important role in the development of immune deficient disorders such as Kaposi's' sarcoma, AIDS or other opportunistic infections because Barton associates immune dysfunction with conditions such as AIDS, Kaposi's' sarcoma etc., and Balsa teaches that activity of MAO-B is predominant in G and L cells , which can be effectively inhibited by deprenyl. One of an ordinary skill in the art would have expected DMS, a monoamine oxidase inhibitor, to be effective in treating AIDS, tumors, cancers and other immune deficient conditions by inhibiting the action of MAO-B of immune cells i.e.,

lymphocytes and granulocytes. While the above references do not explicitly state a reduction in the levels of gamma-IFN, absent showing the evidence to the contrary, it is the position of the examiner that the claimed composition implicitly restores the levels of gamma-IFN. Furthermore, optimization of claimed dosage of DMS and choosing the appropriate routes of administration, with an expectation to obtain the desired therapeutic effect would have been within the scope of a skilled artisan.

Response to Arguments

The terminal disclaimer filed 1-25-05 has been accepted and accordingly the double patenting rejection has been withdrawn.

Applicant's arguments filed 1-25-05 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

Applicants assert that the claims are enabled because it is well within the skill of one in the art to determine whether a condition produced by immune system dysfunction is associated with reduced levels of gamma-interferon production, and whether administering the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in gamma-interferon production. It is argued that the underlying complexity of the immune system does not mean that the pending claims are not enabled and that measuring reduced levels or increased levels of gamma-interferon in a mammal are well within the skill of one in the art, and do not require undue experimentation. Applicants also argue that whether or

not the claims will encompass multiple complex diseases or disorders is irrelevant to the question of enablement, since one of skill in the art will clearly be able to identify conditions produced by immune system dysfunction associated with reduced levels of gamma-interferon production and that one of skill in the art can identify conditions that fall within the genus of conditions produced by immune system dysfunction is associated with reduced levels of gamma-interferon production without undue experimentation, as supported by as Exhibit A, which clarifies the correlation of IFN-gamma to conditions related to immune deficiency such as cancer and AIDS, as well as autoimmune diseases due to the central role of IFN-gamma in the immune system. Adequate function of the IFN-y/macrophage system is essential for natural as well as acquired resistance to infection and cancer. Malfunctioning of the system is recognized to be instrumental in inflammatory and autoimmune disease.

Applicants arguments have been considered but not found persuasive because applicants have not provided nor shown how one of an ordinary skill in the art would readily recognize that a particular condition such as cancer (acute or chronic) or Alzheimer's' or a specific condition in the AIDS syndrome (such as an infection or Kaposi's sarcoma) is always associated with reduced levels of gamma-interferon. Applicants themselves stated that there is an underlying complexity in the immune system function due to the interplay of several interleukins, cytokines, and growth factors. While it is true that reduced gamma-interferon is recognized as the cause of some or certain disease or disordered conditions, there is no guidance in the instant

specification as to how one of an ordinary skill in the art would recognize that it is the levels of gamma-interferon alone that caused the conditions. A person in need of a treatment for a disease or disorder can only recognize the symptoms of the particular disease or disorder, but not the underlying causes. Absent any showing or guidance in the instant specification that the conditions and diseases can only be caused by reduced gamma-interferon and but due to any other underlying cause (for instance an increased tumor necrosis factor or altered levels of any other interleukin or cytokine), why one of an ordinary skill in the art would tend to measure the IFN-gamma levels, when the diseases or disorders can also be caused by other cytokines or cytokines etc. Applicants argue that examiner improperly inserted the limitation of complete treatment of the claimed conditions. While it is true that the treatment does not necessarily mean a cure for the claimed conditions, examiner still maintains the argument that the breadth of the instant "treatment" extends to conditions that are yet to be identified as being associated o caused by reduced levels of gamma-IFN. Besides, applicants also did not provide any guidance or rationale that a reduced gamma-IFN level is necessarily associated with clinical conditions that require treatment and that restoring the gamma-IFN levels provides a therapeutically effective treatment for all the conditions that are associated with reduced levels of IFN. Thus, the specification enables only restoration of gamma-IFN levels by treating with the claimed DMS enantiomer but does not provide guidance to one of an ordinary skill in the art at the time of the instant invention to treat all the conditions associated with the reduced levels of IFN-gamma and provide a therapy for the same.

Claim Rejections - 35 USC § 103

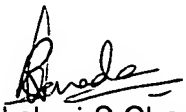
Response: Applicants argue that there is no prima facie case of obviousness established, as there is no motivation or suggestion to combine the reference teachings and no reasonable expectation of success. Applicants argue that the combination of references do not teach or suggest all elements of the pending claims because as the office action also admits the references do not state a reduction in the levels of interferon (a condition that is present in each of the pending claims). Applicants arguments are not persuasive because the claims require a method of treating a condition that is associated with reduced IFN levels and specifically recite AIDS, cancer etc. The claims are not directed to a method of restoring IFN levels and hence condition associated with reduced levels of gamma-IFN is not a positive limitation. Further, it is the position of the examiner that the reduced levels of IFN are implicit in the conditions taught by Barton. This is further supported applicants argument regarding the enablement of instant method (see the above sections), where applicants argued that reduced levels of gamma-IFN plays a role in immune system dysfunction and also provided evidence that conditions such as cancer and AIDS are related to immune deficiency, as evidenced by exhibit A (submitted by applicants in response to enablement rejection of record). Instant specification teaches the claimed compounds as MAO inhibitors, which the cited reference of Borbe also teaches. Further, the motivation to use the compounds of Borbe for treating the immune deficiency related conditions (of Barton) comes from the teaching of Balsa that the same enzyme MAO- in

present in the lymphocytes and granulocytes, the cell types that play a key role in the immune system function (or dysfunction).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lakshmi S Channavajjala
Examiner
Art Unit 1615

May 9, 2005